REMARKS/ARGUMENTS

With entry of this amendment, claims 1-2, 6-8 and 12-17 are pending in the above-identified application. Claims 1, 6, 11-15, and 17 have been amended as set forth in detail below. Support for these amendments is identified in the following remarks. No new matter is added by these amendments. In view of the amendments and remarks set forth herein, examination and reconsideration of all pending claims is respectfully requested.

Rejections under 35 U.S.C. § 112

Written Description

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that the limitation "B7 co-stimulatory molecule" is not defined in the specification and further alleges that the disclosure of B7-1, B7-2, B7-3 and B7H "does not adequately describe the scope of the claimed invention."

While Applicants do not agree with the Examiner's rejection nor reasons for rejection, but in order to further expedite prosecution of the instant application, independent claims 1 and 6 are amended to recite "at least one of a B7-1, B7-2, and B7-3 co-stimulatory molecule." In view of these amendments, dependent claim 11 is amended to avoid redundancy by reciting that the co-stimulatory molecule is "B7-1 or B7-2." Support for these amendments are found in the specification as filed at, *e.g.*, page 4, line 11, to page 5, line 13.

Further, in view of the Examiner's particular objection to the term "B7 co-stimulatory molecule" (and, again, while Applicants do not agree with the rejection), dependent claim 11, which now recites "B7-1 or B7-2," and dependent claim 12, which recites "B7-1," are each amended to delete "B7" from the term "B7 co-stimulatory molecule."

Applicants note that, as of the effective filing date, the structures of B7-1, B7-2, and B7-3 co-stimulatory molecules were well-known in the art. Accordingly, in view of the amendments set forth above, Applicants believe that claims 1, 2, 6-8 and 11-17 as presently amended comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Indefiniteness

Claim 13 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that there is "insufficient antecedent basis" for the limitation "non-viral vector encoding one or more B7 co-stimulatory molecules" in line 2 of the claim.

Claim 13 is amended to delete the phrase "encoding one or more B7 co-stimulatory molecules." Accordingly, claim 13 now recites, *inter alia*, "wherein the peptide antigen and non-viral vector are administered ...." To maintain consistency of claim language, corresponding amendments have been made to claims 14 and 15.

Applicants note that the deleted language is redundant to the extent that the non-viral vector of claim 13 includes all the limitations of the corresponding non-viral vector of claim 6, from which claim 13 depends. Because there is antecedent basis for "non-viral vector" in independent claim 6, the present rejection under 35 U.S.C. § 112, second paragraph, is obviated. Withdrawal of the rejection is respectfully requested.

Enablement

Claims 1, 2, 6-8, and 11-17 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected to, to make and/or use the invention. The present rejection is overcome in part and traversed in part as set forth below.

As an initial matter, Applicants note that the Examiner states that because the claims are drawn to B7-1, B7-2, or B7-3, that it is CTL responses that are enhanced. (*See* Office Action 11/18/2004 at page 7.) In this regard, the Examiner appears to admit that the claims are enabled for enhancing CTL responses. Further, to clarify for the record the role of B7-1, B7-2, and B7-3 in mediating immune responses, and to the extent that the Examiner may be suggesting that the claims are not enabled for enhancing non-CTL immune responses, Applicants note that, in addition to $CD8^+$ CTLs, $CD4^+$ helper T cells (involved in mediating both humoral and cell-mediated immune responses) express receptors for B7-1, B7-2, and B7-3.

Rafiee *et al.*

The Examiner cites to Rafiee *et al.* (*Cancer Gene Therapy* 8:974-981, 2001) as allegedly evidencing non-enablement of the present invention. The Examiner states, *inter alia*, that "Rafiee et al. ... teach that T-cell co-stimulation and antigen presentation are known to be dose-dependent." (Office Action dated 11/18/2004, at page 6.) In particular, the Examiner states, for example, "that a strong signal one does not require signal two, and ... inhibition of signal two in the presence of a strong signal one can actually enhance T-cell stimulation." (*Id.*) Applicants believe that Rafiee *et al.* is insufficient to establish non-enablement of the present claims.

Enablement under 35 U.S.C. § 112, first paragraph, is satisfied where one of skill in the art, in view of the specification's disclosure and the knowledge in the art as of the filing date, would be able to carry out the invention as claimed without undue experimentation. *See* MPEP § 2164. "Experimentation" is not undue where it is considered routine in the context of the claimed invention. *See id.* at 2164.06.

In the present case, the claims recite administration of an "immunogenically effective amount" of the antigen and non-viral vector, *i.e.*, "an amount that is, in combination, effective, at dosages and for periods of time necessary, to elicit a specific T lymphocyte mediated response." (Specification at page 43, lines 9-11.) Assays for determining elicitation of a T cell response, and therefore for confirming appropriate dosages of antigen and vector in accordance with the present invention, were well-known in the art. For example, the specification states that a specific T lymphocyte mediated response "can be determined by conventional assays for T-cell activation, including but not limited to assays to detect specific cytokine activation and/or cytolytic activity." (*Id.* at lines 11-13.)

It is submitted that dosage determination using such assays, as referenced above, is not undue in the context of *in vivo* administration of pharmacological agents. This is particularly true in the instant case. Assuming, *arguendo*, the Examiner's characterization of Rafiee *et al.*, it was well-known as of the effective filing date that mediation of T cell responses via B7 costimulatory pathways was dose dependent. Accordingly, one of skill in the art reading the instant specification and using the methods as claimed would expect to confirm appropriate dosage of antigen and vector for any particular application of the claimed method. As set forth in the MPEP, "[c]laims are not rejected as broader than the enabling disclosure for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art." MPEP § 2164.08.

PROMT Accession No. 1988: 555242

The Examiner continues to cite PROMT Accession No. 1998: 555242 (*Lancet* 24 Oct. 1998, pp. 1323(1)) as evidencing virus variability that allegedly renders the claims non-enabled under 35 U.S.C. § 112, first paragraph. The Examiner states that virus variability would "preclude enhancement of an immune response to a peptide or protein composition if the isolate used to design the peptide or protein composition varies from the clinical isolate currently replicating in vivo."

To the extent that the Examiner contends that some embodiments of the method as claimed may be "inoperative," Applicants note, as discussed in Applicants' previous response (filed 8/6/2004), that this aspect of the rejection goes to utility as it relates to enablement of "how to use" under 35 U.S.C. § 112. In this regard, to the further extent that the Examiner relies on a standard of therapeutic or pharmacological utility, Applicants remind the Examiner that therapeutic or pharmacological inventions satisfy utility under 35 U.S.C. § 101 (and, therefore, the "how to use" requirement under 35 U.S.C. § 112) where "any benefit" is provided to the public. MPEP § 2107.01 (III) (emphasis original).

In view of the above, and notwithstanding "virus variability," the present methods as claimed are enabled under 35 U.S.C. § 112, first paragraph. Applicants have disclosed, in the specification as filed, a physiological effect of administering a peptide or protein antigen coordinately with a non-viral vector encoding at least one of B7-1, B7-2, and B7-3, *inter alia*, elicitation of an immune response that is enhanced relative to that elicited using the peptide or protein antigen alone. It is submitted that the discovery of this physiological effect constitutes identification of a pharmacological activity and, therefore, provides an "immediate benefit" to the public. *See* MPEP § 2107.01 (III) (stating that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement" (emphasis original)). Because "it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, ... adequate proof any such activity constitutes a showing of practical utility." *Id.*, citing *Nelson v. Bowler*, 206 USPQ 881, 883 (CCPA 1980).

Further, Applicants emphasize that enablement under 35 U.S.C. § 112, first paragraph, must be "evaluated against the claimed subject matter." MPEP § 2164.08 (emphasis provided). In the present case, the methods as claimed do not themselves recite enhancement or supplementation of an immune response "to a clinical isolate replicating *in vivo*." What is claimed is elicitation of an immune response against the peptide or protein antigen, comprising one or more T cell epitope(s), that is administered coordinately with the non-viral vector. While

a result of elicitation of this immune response may include enhancement of a response to a clinical isolate replicating *in vivo*, it is not required by the claim itself.

Moreover, Applicants note that eliciting an immune response to an antigen comprising one or more T cell epitope(s) using as the methods claimed, even in the absence of a corresponding clinical isolate replicating *in vivo* in a subject, could be used, *e.g.*, to potentiate a prophylactic effect against a pathogenic agent comprising the one or more T cell epitope(s), whether or not the subject ever actually encounters a pathogenic agent comprising the particular epitopes.

In view of the remarks set forth above, the present claims satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. Withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. § 103

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,942,607 in view of Kaufmann *et al.* (*Cell. Immunol.* 196:246-251, 1996), alleged admitted prior art in the specification on page 37 at lines 7-18, Rock *et al.* (PNAS USA 89:8918-8922, 1992), U.S. Patent No. 5,738,852, and WO 98/04705 and the CAPLUS Accession No. 1998: 106018 summary of said document. This rejection is overcome in part and traversed in part.

Independent claims 1 and 6 as amended recite that "the non-viral vector and [peptide or] protein antigen are administered separately to closely adjacent sites." Support for this amendment is found in the specification as filed at, *e.g.*, page 42, lines 24-29. Dependent claims 14 and 15 have been amended accordingly to avoid redundancy.

Applicants submit that a *prima facie* case of obviousness has not been established with respect to the claims as presently amended. In particular, the Examiner has not shown

where the cited art teaches or suggests administering the non-viral vector and peptide or protein antigen "separately to closely adjacent cites." Thus, the Examiner has not established a teaching or suggestion of all claim limitations in the cited art, as required under MPEP § 2143.

As of the effective filing date of the instant application, it had been shown in the art that co-stimulatory molecules and antigen need to be on the same antigen presenting cells to increase the T cell response. The cited references accomplish this either by modifying the cells *ex vivo* to express both antigen and co-stimulatory molecule, followed by use of the transfected cells as a vaccine, or by injecting vectors expressing both, either as one vector or a mix of vectors, into the host together. In addition, it was known to those in the art from long-standing literature on transfection of cells that transfecting with two vectors simultaneously typically results in the uptake of both vectors or uptake of neither vector by the same cells, but not uptake of just one vector. It was not known whether administering a non-viral vector (expressing a co-stimulatory molecule like B7-1, B7-2, or B7-3) separately to a site closely adjacent to a site of injection of a peptide or protein antigen would accomplish the goal of transfecting the same cells with the vector that also take up and express the antigen on their MHC molecules.

For the reasons stated above, there is no teaching or suggestion in the cited art that administration of vector and antigen "separately to closely adjacent sites" would be suitable for the intended purpose of enhancing or supplementing an immune response. Neither (a) the use of cells transfected *ex vivo* with DNA encoding both antigen and costimulatory molecules (*see, e.g.,* Kaufmann *et al.*; U.S. 5,942,607), nor (b) the injection together of vectors expressing such DNA (*see, e.g.,* U.S. 5,738,852), which are expected to be taken up and expressed, if at all, by the same cells, teach or suggest that separate administration of antigen and a non-viral vector expressing the co-stimulatory molecule would accomplish the goal of achieving antigen presentation and vector expression in the same antigen present cells (and, therefore, of increasing immunogenicity of the antigen). Therefore, Applicants believe claims 1, 2, 6-8, and 11-17 to be non-obvious over the cited references under 35 U.S.C. § 103. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 18 May 2005 By: Brian W. Poor

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